REVIEW

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Switching from Brand-Name to Generic Psychotropic Medications: A Literature Review

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SUMMARY

Generic medications do not undergo the rigorous approval process required of original medications. Their effectiveness and safety is expected to be equal to that of their more expensive counterparts. However, several case reports and studies describe clinical deterioration and decreased tolerability with generic substitution. Pubmed was searched from January 1, 1974 to March 1, 2010. The MeSH term "generic, drugs" was combined with "anticonvulsants," "mood stabilizers," "lithium," "antidepressants," "antipsychotics," "anxiolytics," and "benzodiazepines." Additional articles were obtained by searching the bibliographies of relevant references. Articles in English, French, or Spanish were considered if they discussed clinical equivalence of generic and brand-name medications, generic substitution, or issues about effectiveness, tolerability, compliance, or economics encountered with generics. Clinical deterioration, adverse effects, and changes in pharmacokinetics are described with generic substitution of several anticonvulsants/mood stabilizers (carbamazepine, valproate, lamotrigine, gabapentin, topiramate, lithium), antidepressants (amitriptyline, nortriptyline, desipramine, fluoxetine, paroxetine, citalopram, sertraline, venlafaxine, mirtazapine, bupropion), antipsychotics (risperidone, clozapine), and anxiolytics (clonazepam, alprazolam). Generics do not always lead to the anticipated monetary savings and also raise compliance issues. Although the review is limited by publication bias and heterogeneity of the studies in the literature, we believe there is enough concern to advise generic switching on an individual basis with close monitoring throughout the transition. Health professionals should be aware of the stakes around generic substitution especially when health economics promote universal use of generics.

Introduction

Generic formulations of brand-name medications can enter the American, Canadian, and European markets 20 years after the appearance of the original compound [1,2]. The Canadian Generic Pharmaceutical Association [1] claims that the quality, purity, effectiveness, and safety of generics are equivalent to their more expensive original counterparts. The process of approving generic medications is not as rigorous as that of brand-name medications and studies and case reports have raised concerns over the true equivalence of generic and brand-name medications.

Bioequivalence between generic and original medications is determined by comparing bioavailability of formulations [3]. The area-under-the-curve of the drug concentration–time curve (AUC) and the maximum plasma concentration (C_{max}) of the drug are measures of bioavailability. Most regulatory agencies require that the 90% confidence intervals (CI) of the generic-to-reference compound log-transformed AUC and C_{max} ratios fall within 80% and 125% for two compounds to be considered bioequivalent [4–6]. Two generics of the same compound can theoretically have a 45% difference in AUC and C_{max} ratios. Such variations can become important with medications that are poorly soluble, have a narrow therapeutic index or have non-linear kinetics, or may induce or inhibit hepatic microsomal enzymes such as anticonvulsants [3,7].

Whether bioequivalence reflects clinical equivalence is controversial. In a previous article [8], we suggested that lack of appropriate studies involving generics and differences in excipients across generics partly explain the different clinical responses and side effects observed with generic and original medications. Insufficient resources to ensure adequate postmarketing monitoring of generics is also hypothesized as contributing to lower quality of generics [9].

Not all studies comparing generics to brand medications have found differences. For instance, a recent systematic review and meta-analysis [10] suggested that most cardiovascular generic medications are clinically equivalent to their brand counterparts. Conversely, studies with medications used in neurology,

psychiatry, and transplantation medicine [6] reveal concerning differences between formulations. This article reviews studies and case reports exploring the clinical equivalence between generic and original psychotropic medications, especially issues reported with generic formulations, which are summarized in Table 1.

Methods

The literature was searched through Pubmed from January 1, 1974 to March 1, 2010. The MeSH term "generic, drugs" was combined with "anticonvulsants," "mood stabilizers," "lithium," "antidepressants," "antipsychotics," "anxiolytics," and

Table 1 Issues reported in patients with generic formulations of psychotropics

Anticonvulsants and/or mood stabilizers		Reference
Anticonvulsants	Patients with epilepsy requiring acute care are more likely to have had change in formulation in the 6 months prior	[13,14]
Carbamazepine	Increased seizures after generic substitution	[12,15–18]
	Decreased levels after generic substitution	[12,16,17]
	Toxicity and increased levels after generic substitution	[19,20]
	Adrenal decompensation after generic substitution in a patient on hydrocortisone	[21]
	90% CI of AUC of generic not within 80–120% of original.	[22]
	Shorter average time to C_{max} with generic	[23]
	More neurological side effects with generic	[25]
	Shorter mean time to change of medication, more central nervous system side effects with generic	[27]
Valproic acid and derivatives	Decreased levels and increased seizures postswitch from original divalproex sodium to generic valproic acid	[12]
	Increased levels and decreased seizures postswitch from generic to original sodium valproate	[28]
	Seizure postswitch from original to generic valproic acid	[29]
	Depressive symptoms and vague suicidal thoughts postswitch from original divalproex sodium to generic valproic acid.	[8]
	More side effects (esp. gastrointestinal) with generic valproic acid than original divalproex sodium	[32–35]
	Decreased platelets after switch from divalproex sodium to valproic acid	[36]
	Decreased trough levels postswitch from original divalproex sodium to generic valproic acid	[37]
Lamotrigine	Increased seizures and/or side effects after generic substitution	[41]
	Increased seizures and decreased AUC after generic substitution	[43]
	Increased seizures and decreased Cmax postswitch from generic to original lamotrigine	[43]
	Toxicity and increased Cmax after generic substitution	[43]
	Toxicity and earlier Tmax after generic substitution	[43]
	Anticonvulsant hypersensitivity syndrome after generic substitution	[42]
	More antiepileptics and other medications prescribed, and increased dosages with generic substitution	[44–45]
	More frequent out-patients visits and longer hospitalizations with generic substitution	[44]
Gabapentin	Increased seizures after generic substitution	[12]
Topiramate	More antiepileptics and other medications prescribed, higher hospitalization rates, longer hospital stays during periods of multiple generics	[46]
	Generic-to-generic switch associated with increased risk of head injury or fracture	[46]
Lithium	Subtherapeutic blood levels after generic substitution	[47]
Antidepressants		Reference
Amitriptyline	Worsening of depression and decreased blood level following substitution	[48]
	Cessation of agitation postswitch from generic to original	[49]
Nortriptyline	Severe intoxication following substitution from generic to original	[50]
Desipramine	Improvement of depression postswitch from generic to original	[49]
Fluoxetine	More anxiety and diarrhea with generic	[51]
	Relapse of OCD with generic substitution	[53]
	Allergic reactions to generic but not to original	[54]
	Relapse/worsening of depression and/or increased side effects with generic substitution	[8,52,55,56]
Paroxetine	Increased psychiatric symptoms after substitution	[58]
Citalopram	Adverse effects after generic substitution	[57]
	Increased psychiatric symptoms or relapses following generic substitution	[57,58]
Sertraline	Adverse effects after generic substitution	[59]
Venlafaxine	90% CI of C_{max} not within 80–125% of original, more side effects, greater peak-trough variation with generic	[6]
Mirtazapine	Worsening of depression following generic substitution	[8]
Bupropion	Loss of efficacy and/or increased side effects after generic substitution	[60]

Table 1 continued

Antipsychotics		Reference
Chlorpromazine	More dosage adjustments with generic	[62]
Thioridazine	Behavioral changes after generic substitution	[63]
	Adverse effects after substitution	[64]
Clozapine	Relapses or exacerbations after generic substitution	[67,68,69]
	90% CI of mean log-transformed C_{max} not within 80–125% of original	[66]
	Dosage adjustments required after generic substitution	[73,76–79]
Risperidone	90% CI of mean ratios of generic oral solution not within 80–125% of original tablets	[81]
Anxiolytics		Reference
Clonazepam	Increased sedation and anxiolysis with a generic	[83]
Alprazolam	Relapse of panic disorder after generic substitution	[84]

"benzodiazepines." Additional articles were obtained by searching the bibliographies of relevant references. Articles written in English, French, or Spanish were considered if they discussed clinical equivalence of generic and brand-name medications, generic substitution, or issues about effectiveness, tolerability, compliance, or economics observed with generics. Given the wealth of material published on anticonvulsants, we concentrated our search on anticonvulsants that are commonly used in psychiatry, namely carbamazepine, valproate, lamotrigine, gabapentin, and topiramate. We excluded pharmacokinetic studies conducted with healthy volunteers unless they contained important data relevant to the clinical population. Surveys were also excluded.

Substitution of Psychotropics

Anticonvulsants and/or Mood Stabilizers

Harmful effects of switching patients with epileptic disorders from original to generic anticonvulsants have been described, especially with valproate, phenytoin, carbamazepine, and primidone [7,11,12]. Consequently, several European countries announced policies forbidding substitution of anticonvulsant medications [11]. A recent case-control study [13] involving 416 cases who required ambulance, emergency, or inpatient care for an epilepsy-related event matched with 1248 controls who were seeing a doctor in ambulatory setting for epilepsy showed that cases were more likely to have had a switch of their anticonvulsant to another formulation in the 6 months preceding the event (OR 1.81; 95% CI = 1.25–2.63; $P = 0.0024$). The medications most often switched were zonisamide, phenytoin, gabapentin, and clonazepam. Another case-control study [14] involving 991 cases and 2973 matched controls produced similar results (OR of antiepileptic drug substitution in the 6 months prior to event: 1.84; 95% CI = 1.44–2.36).

Carbamazepine

Several authors reported increased seizures [12,15–17] and lower carbamazepine levels without changes in dosages [12,16,17] after patients changed from brand-name to generic carbamazepine. Jain et al. [18] studied 299 cases of seizures with carbamazepine therapy registered at Ciba-Geigy from 1976 to 1990. Out of 131 cases with adequate information, 27 appeared to result from a switch between brand-name and generic carbamazepine. Berg et al. [12] reviewed the charts of 50 epileptic patients who experienced seizures following generic substitution of anticonvulsants. Seven of these cases involved generic substitution of Tegretol, Tegretol XR, or Carbatrol and carbamazepine levels were decreased by 20% on average at the time of the seizure compared to the preswitch level. Most patients were switched-back to the branded formulation with good results.

Toxicity has also been described following switch from original to generic carbamazepine. Up to threefold increases in carbamazepine levels were measured postsubstitution [19,20]. Vergely et al. [21] described a patient with epilepsy and Addison's disease who was admitted with adrenal decompensation 3 months after brand-name carbamazepine was switched to generic. Higher carbamazepine levels postswitch may have led to increased metabolism of hydrocortisone and subsequent adrenal decompensation.

Clinical studies have shown different pharmacokinetics between original and generic carbamazepine. Silpakit et al. [22] conducted a double-blind randomized three-phase crossover study of brand-name carbamazepine and 3 generics in 18 adults suffering from epilepsy. Only two of the three generics, Carmapine and Carzepine, had 90% AUC CI falling between 80% and 120% of original carbamazepine. Oles et al. [23] did not find significant differences between Tegretol and the generic carbamazepine Epitol in seizure frequencies, AUC, and C_{max} in their randomized double-blind crossover trial of 40 epileptic patients, but noted shorter average time to C_{max} with Epitol.

However, Aldenkamp et al. [24] found no significant differences in the pharmacokinetics of Tegretol and two generic formulations, carbamazepine Pharmachemie, and carbamazepine Pharbita, in a randomized open-label observer-blind crossover trial involving 12 patients with epilepsy. No significant differences in cognitive function were observed between the three formulations.

Different formulations of carbamazepine may nonetheless lead to different side effects. Hartley et al. [25] studied original

carbamazepine and a generic from Ethical Generics in 23 children with epilepsy. Seizure rates and plasma levels were not significantly different. However, the generic formulation caused significantly more neurological side effects. In a later study, Hartley et al. [26] showed that the bioavailability and pharmacokinetics of Tegretol and a generic of carbamazepine were not significantly different in 12 children with epilepsy. Garnett et al. [27] found that patients on a generic formulation of carbamazepine had a shorter mean time to change of medication compared to patients on original carbamazepine. Patients on generic also experienced more central nervous system side effects and higher epilepsy-related medical costs at 1 year.

Valproic Acid and Derivatives

Sodium valproate is the sodium salt of valproic acid. Divalproex sodium contains sodium valproate and valproic acid in a 1:1 molar relationship. Valproic acid and divalproex sodium are often used interchangeably. Berg et al. [12] reported on 14 patients who developed seizures after brand-name divalproex sodium, Depakote or Depakote ER, was changed for generic valproic acid. Valproic acid levels were reported before and after substitution for eight of these cases; all showed a decrease with an average decrease of 34%. Most patients regained control of seizures after switching-back to the original medication. Dhanaraj and Jayavelu [28] described two patients with mental retardation and epilepsy who had fewer seizures and higher plasma levels after their generic sodium valproate was changed to original at the same dose. MacDonald [29] reported on a woman seizure-free for 3 years who developed a seizure 3 days after Depakene (taken in combination with carbamazepine) had been changed to generic. Our group [8] reported on a 45-year-old male with paranoid schizophrenia stable on Risperdal Consta, original divalproex sodium (Epival), procyclidine, and olanzapine, who became depressed with vague suicidal thoughts 3 weeks after Epival was switched to generic valproic acid (Apo-valproic). His symptoms improved within 9 days of switching back to Epival.

On the other hand, Vadney and Kraushaar [30] randomized 64 patients with mental retardation and epilepsy to receive 4 weeks of original valproic acid, Depakene, or generic valproic acid marketed by Solvay Pharmaceuticals. Groups were crossed-over for an additional 4 weeks. No significant changes in seizures or blood levels were reported. Authors concluded that generic valproic acid could be safely used in this population and may lead to considerable monetary savings. Iqbal et al. [31] compared 4036 patients with bipolar disorder on branded divalproex sodium monotherapy to 588 patients with bipolar disorder on generic valproic acid monotherapy in a retrospective study using Veterans Affairs databases. They found no significant differences in persistence with medication, risk of hospitalization and time to event between the two groups.

Increased rates of gastrointestinal side effects with generic valproic acid have been described [32–35]. One case report [36] found decreased platelets following a switch from divalproex sodium to valproic acid, normalizing after switch-back to divalproex sodium. Zarate et al. [34] retrospectively examined charts of 300 hospitalized psychiatric patients treated with divalproex sodium or valproic acid. Both medications were equally efficacious but carried different rates of gastrointestinal side effects; 14.7% for divalproex sodium and 28.7% for valproic acid. A chart review of 28 patients with psychotic disorders switched from divalproex sodium to valproic acid did not show a difference in effectiveness [35]. Valproic acid was, however, prescribed at higher doses and was associated with more gastrointestinal side effects.

Other authors have expressed fewer concerns over differences in gastrointestinal side effects. Sherr and Kelly [37] followed 47 psychiatric in-patients treated with original divalproex sodium, Depakote, for at least 1 month. Patients switched to generic valproic acid at the same dose. At 2 weeks, no changes in Clinical Global Impression (CGI) score or seizure incidence were reported and only one patient switched back due to persistent gastrointestinal effects. Trough concentrations were however decreased by 14.4% at 2 weeks compared to baseline. Citrome et al. [38] reported that the 14 day-discontinuation rates for valproic acid and divalproex sodium were similar in cohorts of 3536 and 4942 psychiatric in-patients, in 1994 and 1996 respectively, refuting a dramatic difference in side effects.

Some authors have concluded that switching from divalproex sodium to valproic acid is a worthwhile effort. Wagner et al. [39] reported successful mass substitution from divalproex sodium to valproic acid in 2 facilities; 46 patients of a developmental center and 52 patients of a correctional facility were involved. In the first facility, no significant fluctuations in serum levels 2 and 4 weeks after substitution were noted. In the second, four patients had gastrointestinal side effects following substitution, and one switched back to divalproex sodium. Both facilities reported considerable monetary savings. Cranor et al. [40] performed a chart review of institutionalized adults with mental retardation and epilepsy. Data was analyzed for 46 patients stable on divalproex sodium who switched to valproic acid. Substitution was effective in 89% of patients and led to considerable cost savings. Wassef et al. [33] studied 5228 psychiatric patients started either on original divalproex sodium (Depakote) or generic valproic acid during hospitalization. They estimated that 6.4% more patients could not tolerate valproic acid due to adverse effects, mostly gastrointestinal, than divalproex sodium. They concluded that valproic acid should be prescribed first, given potential cost savings, and changed for delayed-release divalproex sodium if not tolerated.

Newer Anticonvulsants: Lamotrigine, Gabapentin, and Topiramate

Makus and McCormick [41] asked pharmacists in Ontario for Health Canada adverse-reaction forms that physicians filled to allow patients who suffered adverse reactions upon generic switching of lamotrigine to switch back to Lamictal. Fourteen adverse-reaction forms were provided by 71 different pharmacies. The reason cited for switch-back to original lamotrigine was loss of seizure control in 11 cases (79%), with concomitant anxiety, mood swings, and dizziness in one of these cases. Other cited reasons were agitation and insomnia in one case (5%), headaches in one case (5%), and bad taste in one case (5%). Seizure control

was reestablished upon switch-back to original lamotrigine in 8 of the 10 cases where outcome information was provided.

Sabroe and Sabers [42] described the case of a 29-year-old male with refractory epilepsy who developed anticonvulsant hypersensitivity syndrome, a potentially lethal condition, 8 weeks after the original lamotrigine he had been taking for 10 years was changed to lamotrigine Copyfarm, a generic, at the same dose of 800 mg/day. After 3 weeks of hospitalization, he was switched back to original lamotrigine and his symptoms disappeared within 6 weeks. Plasma concentration levels were the same with both formulations. A new or unknown impurity not present in the original formulation was found in the generic and hypothesized as the cause of the syndrome.

Nielsen et al. [43] reported on nine patients who requested pharmacokinetic monitoring through switching of lamotrigine formulations. The C_{max} of a patient who experienced ataxia and falls resulting in a skull fracture and epidural hematoma was 21% higher once his Lamictal was switched to lamotrigine Copyfarm. The AUC of a patient who complained of seizures and vertigo after Lamictal was changed to lamotrigine Copyfarm was 13% lower. The C_{max} of a patient switched from lamotrigine Actavis to Lamictal who relapsed after having been seizure-free for 1.5 years was 17% lower. Pharmacokinetic deviations were also apparent in a patient who experienced status epilepticus after Lamictal was changed repetitively to three different generics. A patient with temporary ataxia had an earlier T_{max} on lamotrigine Strada than on Lamictal. The other patients exhibited full bioequivalence or their complaints could not be confirmed by pharmacokinetic parameters.

Berg et al. [12] described eight cases of breakthrough seizures in epileptic patients following generic substitution of Neurontin. All switched back to original gabapentin with control of seizures documented for most of them.

Studies [44–46] have reported higher switch-back rates following generic substitution of antiepileptics than substitution of other commonly prescribed medications. A switch from Lamictal to generic lamotrigine has been associated with mean increases in dose of 5.1% and 6.2%, in Quebec and Ontario, respectively [44,45]. Availability of generic lamotrigine has also been associated with an increased number of other anticonvulsants and other medications prescribed for the same patients including levothyroxine, acetylsalicylic acid, folic acid, risperidone, and lorazepam. In Quebec, it was further linked to more frequent outpatient visits, and longer hospitalizations. Period when multiple generic versions of topiramate were available was associated with more prescriptions for other anticonvulsants as well as other medications, higher hospitalization rates, longer hospital stays, and higher annualized health care costs in Quebec than brand-use period [46]. Generic-to-generic topiramate switch was associated with a 2.8-fold increase in risk of head injury or fracture [46].

Lithium

Pakes [47] reported two cases where generic substitution of brand-name lithium (Eskalith and Lithane) led to subtherapeutic blood levels. One patient had levels of 0.8 meq/L on brand-name lithium (Eskalith) and 0.4 meq/L 1 week after substitution to a generic marketed by Philips Roxane.

Antidepressants

Amitriptyline, Nortriptyline, and Desipramine

Substitution of antidepressants has been a source of concern. Ostroff [48] described a 56-year-old man with depression controlled with 150 mg of amitriptyline. Symptoms of depression reappeared when amitriptyline was switched unknowingly to another formulation, which incited the physician to increase dosage to 250 mg. Blood levels were higher with 150 mg of the first formulation than with 250 mg of the second. The patient improved once returned to the first amitriptyline formulation. Schnur reported cessation of agitation when generic amitriptyline in an elderly patient was changed to Elavil [49]. Dubovsky [50] reported a case of severe nortriptyline intoxication when a patient was changed from a generic to the brand-name formulation without his knowledge. Schnur described a 97-year-old patient who developed anorexia, depression, and lethargy on generic desipramine. The medication was changed to Norpramin at the same dose and the patient became alert, oriented, and cheerful [49].

Fluoxetine

In a double-blind crossover study [51], generic fluoxetine (Novofluoxetine) was found to cause more anxiety and diarrhea than original fluoxetine (Prozac). The original led to a non-significant improvement on the Hamilton Depression Rating Scale in depressed patients. In Switzerland, relapse of depression [52] and relapse of obsessive–compulsive disorder [53] were reported following generic substitution of fluoxetine. In both cases, patients improved after returning to original medication. In two other cases, patients experienced allergic reactions to generic fluoxetine but not to original [54]. Yu [55] reported on six patients where a switch from Prozac to a generic manufactured by Barr Laboratories was associated with worsening depressive symptoms and/or increased side effects. The literature contains at least one other report of relapse of depression following a switch from Prozac to generic fluoxetine [56].

Fluoxetine and Mirtazapine

Our group [8] reported on two women whose depressive symptomatology worsened when their antidepressant was switched from original to generic. In the first, Prozac was substituted by PMS-fluoxetine and in the other, Remeron was replaced by Genmirtazapine. Both patients improved once their original medication was reinstituted.

Citalopram

Van Amerigen et al. [57] described 20 cases of relapse or new adverse events after Gen-citalopram was unknowingly substituted for Celexa. All patients improved following reinstitution of their brand-name medication.

Citalopram and Paroxetine

Rosenthal et al. [58] described seven patients who had an increase in symptoms or a relapse after a change in the formulation of their antidepressants. Six patients had been switched from brand paroxetine or citalopram to a generic formulation whereas one had been switched from one generic paroxetine to another.

Citalopram and Venlafaxine

Chenu et al. [6] measured citalopram plasma levels in volunteers on Gen-citalopram and Celexa. There were no significant differences between the two groups at all measurements. Venlafaxine plasma levels were however significantly higher in volunteers taking Novo-venlafaxine XR as opposed to Effexor XR at 240, 300, and 360 min, after day 1 and day 5. Volunteers on generic venlafaxine also experienced significantly more side effects. The 90% CI for the C_{max} ratio of generic to brand-citalopram was between 97% and 100%. The average C_{max} ratio of generic to brand-venlafaxine was 150% with a 90% CI of 104–217%, failing to meet standards of many regulatory agencies. The one-size spheres of Novo-venlafaxine XR compared to the three-sizes spheres of Effexor XR were hypothesized as being responsible for a pharmacokinetic profile more representative of an "intermediate" release formulation than of a true extended release. Chenu et al. [6] suggested that greater peak to trough variation obtained with generic venlafaxine possibly affects effectiveness.

Sertraline

Miller [59] described a patient switched from Zoloft to a generic who, within weeks, developed uncomfortable warmth and flushing lasting a few minutes every time he took the medication. Side effects subsided when the dose of generic sertraline was lowered.

Bupropion

The FDA reviewed bioequivalence studies of Wellbutrin XL and Budeprion XL marketed by Teva after it received, between January 1 and June 30, 2007, 85 postmarketing reports of adverse effects in patients where Budeprion XL 300 mg was substituted to Wellbutrin XL 300 mg [60]. Loss of efficacy was reported in 78 of these cases. Appearance or worsening of side effects was also reported. Improvement in side effects and depression ensued in more than half of the patients who returned to the original medication. After its review, the FDA concluded that the two formulations were equivalent. Bioequivalence studies were however only performed with tablets of 150 mg due to concern of inducing seizures in volunteers [60].

Antipsychotics

First-Generation Antipsychotics

Concerns about nonequivalence of branded and generic antipsychotics date back to the 1970s with the expiration of the patents of earliest compounds. In 1974, Simpson et al. [61] concluded that two formulations of chlorpromazine were bioequivalent after studying 50 patients with chronic schizophrenia and monitoring their blood levels, psychiatric symptoms, and extrapyramidal symptoms. In 1976, Chien et al. [62] showed that generic chlorpromazine was clinically equivalent to Thorazine in 54 hospitalized patients. Although not statistically significant, patients on generic chlorpromazine received on average a 21% higher dosage than patients on Thorazine. Patients on the generic required more dosage adjustments. In the 1980s, concerns were raised about bioequivalence of generic preparations of thioridazine which were approved mostly based on single-dose bioavailability studies [63,64]. The case of an elderly woman exhibiting behavioral changes after Mellaril was changed to generic was reported [63]. Weber and Wagner [64] randomized five in-patients stable on a formulation of thioridazine to receive either the original or one of two thioridazine generics. Two young men with schizophrenia developed unprovoked outbursts and significant drowsiness, respectively, following substitution. These effects subsided after thioridazine was changed to another formulation.

A double-blind randomized study [65] compared the clinical efficacy of generic fluphenazine decanoate with the original product in patients with schizophrenia. Both groups had a median change of zero in Positive and Negative Syndrome Scale (PANSS) scores over 12 weeks, suggesting no difference in effectiveness between the two products.

Clozapine

There are many concerns about the interchangeability of clozapine. Relapses are described with several formulations of generic clozapine. FDA allowed generic equivalence testing performed with 12.5 mg, whereas only 25 and 100 mg tablets are approved [66,67]. Different rates of absorption for brand medication and generics have been hypothesized because the weight ratio of their respective 25 mg tablets to their 100 mg tablets differ [66].

Alvarez et al. [68] described a 79-year-old man with schizophrenia, stable for several years on Clozaril, admitted with a relapse 1 month after Clozaril was replaced by a generic from Mylan Pharmaceuticals. The patient was eventually switched-back to Clozaril and restablized after 2 months.

Lam et al. [66] randomly assigned patients with schizophrenia, stable on Clozaril, to 2 weeks of generic clozapine manufactured by Zenith Goldline Pharmaceuticals or continued treatment with brand-name medication with crossover to the other treatment for another 2 weeks. They only reported on the 21 patients who completed the study. The 90% CI for the mean log-transformed AUC ratio lied between 80% and 125% whereas the 90% CI for the mean log-transformed C_{max} did not. Moreover, one patient had generic-to-brand AUC and C_{max} ratios of less than 54% and 55%, respectively. This particular patient had a 29% increase in his PANSS score while on the generic.

Mofsen and Balter [69] reported on seven cases of relapse, five of which led to hospitalization, when 25 patients of a residential facility were unknowingly switched from Clozaril to the Zenith Goldline generic. Milder exacerbations were reported in six additional patients.

Kluznik [67] randomized 45 patients on Clozaril to either continue treatment or switch to the Zenith Goldline generic for 8 weeks. Treatment groups were crossed over for another 8 weeks. Five patients relapsed and nine worsened without relapsing when switched to generic. Two worsened after switching to the original medication. Although results on the Brief Psychiatric Rating Scale (BPRS) favored Clozaril, results on the Beck Depression Inventory (BDI) favored the generic.

Studies have however reported successful substitution of Clozaril by generic clozapine. Makela et al. [70] reported on 18 of 20 patients switched from Clozaril to the Mylan generic. No clinically significant changes were noted on the PANSS. A 21% reduction on the Beck Anxiety Inventory (BAI) was obtained with the generic but pre- and postswitch BAI scores were both below the threshold of an anxiety disorder.

Sajbel et al. [71] followed 17 patients through conversion from Clozaril to the Zenith Goldline generic. There were no differences in white blood cell (WBC) count, dosages, and adverse effects 4 months postswitch but psychiatric symptoms were not monitored with rating scales.

Bellnier et al. [72] compared Clozaril and a generic in 41 hospitalized patients. Scores on the PANSS did not differ significantly between the two groups. Blood concentrations were also similar.

Krishnan et al. [73] described nonsignificant changes in BPRS scores and clozapine levels in 43 hospitalized patients after generic substitution. Two patients required a dose increase because of irritability.

No decompensations, switch-backs, adverse hematological effects, and no significant changes in clozapine levels were reported by Miozzo et al. [74] during the 6 month follow-up of 71 outpatients changed from Clozaril to a generic.

Sonnenberg et al. [75] reported no significant differences in CGI-Severity scores, mean clozapine dosage, or clozapine levels following generic substitution of Clozaril in 200 patients of one facility.

Alessi-Severini et al. [76] conducted a retrospective chart review of 58 outpatients with psychotic disorders stabilized on branded-clozapine and switched to Gen-clozapine. Data were analyzed for the 6 months preceding and following the switch. The switch did not have a significant impact on the mean doses used, number of physician visits, hospitalization rates, and was not associated with increased adverse effects, including decreases in WBC and neutrophils counts. However, one patient had his dose decreased because of side effects whereas six had their dose increased due to clinical deterioration.

Paton [77] followed 337 patients with schizophrenia 1 month before and 3 months after a switch from Clozaril to Zaponex, a generic manufactured by IVAX Pharmaceuticals. Patients treated with Clozaril for less than 18 weeks at the time of the switch had their dose significantly increased (mean: 327 mg before, 380 mg after). According to CGI scores, 193 patients stayed the same, 92 improved and 19 deteriorated.

Healy et al. [78] followed 125 patients with schizophrenia switched from Clozaril to the Mylan generic. Serum levels taken 2 weeks after the transition did not significantly differ from levels obtained 2 weeks prior to the switch. After substitution, clozapine dosage was increased in 16 patients, and decreased in 11. Psychiatric symptoms were not rated. The dose of an adjunct antipsychotic was decreased in six patients whereas an adjunct antipsychotic was added in nine cases. Emergency room visits decreased in the year following the transition compared to the year before. There were no significant differences in inpatient hospital days, partial hospital admissions, and outpatient psychiatrist visits. Furthermore, the switch was cost-effective.

Stoner et al. [79] converted 24 in-patients from Clozaril to the Zenith Goldline generic after 2 weeks of observation and followed them for 3 months. Mean clozapine dose did not change significantly despite five patients requiring an increase. At 3 months, 10 patients had an increase in BPRS whereas 14 had a decrease. On the CGI-Improvement scale, 18 patients were rated as clinically unchanged or improved compared to six who were described as worse ($P = 0.001$). One patient stopped generic clozapine due to neutropenia but had experienced a similar incident on the original. One patient suffered a pulmonary embolism postswitch. No consistent changes in adverse effects were reported. The authors judged the switch successful.

A recent review [80] pointed out that the IVAX and Zenith Goldline generics are now both marketed by Teva and that several of the above studies had methodological limitations. These authors recommend that generic substitution be done with caution, with the patient and caregiver's knowledge and with documentation of pre- and postsubstitution clinical status and clozapine levels.

Risperidone

A study [81] in the Netherlands comparing the pharmacokinetics of a generic oral solution of risperidone to Risperdal tablets showed that the 90% CI for the mean ratios were not within the acceptable range of 80–125%.

Olanzapine

Araszkiewicz et al. [82] retrospectively reviewed the charts of 85 patients with schizophrenia who had been prescribed Zyprexa or generic olanzapine between 2000 and 2007 in Poland. They analyzed patients according to three groups; those prescribed Zyprexa who remained on it, those initially prescribed Zyprexa but then switched to a generic and those first prescribed a generic. The average dose, frequency of outpatient visits, side effects and rates of relapses were similar for the three groups. The 25 patients switched to the generic did not have a significant change in their dosage or an increase in relapses following substitution.

Anxiolytics

Clonazepam

Rapaport [83] suggested that generic clonazepam causes greater sedation and anxiolysis than the original. He described a patient with panic attacks, symptom free with fluoxetine, and original clonazepam, who complained of fatigue and dizziness after clonazepam was switched to generic without her knowledge. Her symptoms disappeared after she restarted original clonazepam. Rapaport described another woman with panic disorder who

responded well to generic clonazepam. Her anxiety worsened after generic clonazepam was substituted by the original, leading to a dose increase. Substitution was discovered after the patient complained of sedation. A switch-back to the generic at the previous dosage led to resolution of side effects.

Alprazolam

Ross [84] reported the case of a 56-year-old woman with severe panic disorder controlled with 0.5 mg of original alprazolam four times a day who experienced panic attacks on generic alprazolam. Her symptoms remitted completely after she was switched back to Xanax.

Economical Considerations

Generic substitution is not always as economically profitable as expected. Following the compulsory switch from original to generic lamotrigine in Ontario, Duh et al. [85] calculated actual monthly savings of $11.98 per patient as opposed to the expected $30.55. Lamotrigine dosage changes, increased pharmacy utilization, and increased costs of other medications, including other antiepileptics, were responsible for lower than expected cost savings. Based on data from Quebec's health plan, Lelorier et al. [86] showed an increased yearly cost from $6419 to $7902 (Canadian dollars) during generic lamotrigine use period compared to brand-use period. Authors also hypothesized increased costs in the United States with generic lamotrigine. Duh et al. [87] concluded in a recent review that periods of generic anticonvulsants use are associated with higher overall health care costs than periods of brand-name use in Canada and the United States. Using data from Quebec's health plan, Paradis et al. [88] concluded that periods when generic topiramate was available were associated with increased medication dispensing (non-anticonvulsants as well as other anticonvulsants), hospitalizations, increased length of hospitalizations, and increased cost of $1060 (Canadian dollars) per person-year (excluding cost of topiramate). Authors hypothesized higher health care costs for France, Germany, Italy, and United Kingdom following the entry of generic topiramate based on results obtained in Canada.

A Spanish pharmacoeconomic study [89] hypothesized that if 9% of epilepsy patients treated with original carbamazepine were switched to generic carbamazepine, annual per-patient cost would rise 38-fold due to increased seizures causing accidents and deaths and requiring emergency visits and days off work.

In Canada, Layton and Barbeau [90] determined that switching patients from original to generic clozapine would lead to no cost savings if it were accompanied by an 11.2% absolute difference in relapse incidences between the two formulations. A difference in relapse incidences of 28% would cost $1857 annually per patient whereas no difference in relapse incidences would result in annual cost savings of $1241 per patient.

A recent German pharmacoeconomic study [91] predicted that it would be cost-effective to keep patients with schizophrenia on Risperdal, even if the generic was 40% cheaper, if switching to generic risperidone resulted in a 5.2% decrease in compliance.

Formularies or lists of drugs covered for reimbursement usually prefer generic medications to more expensive brand ones. Horn et al. [92], in their study examining the relationship between cost containment strategies and overall health care costs for different medical illnesses, found that more restrictive formularies led to higher overall care costs. There was an association between formulary restrictiveness and utilization of care.

Compliance

Compliance with psychotropic medications is often an issue [93]. Patients with schizophrenia may be suspicious or even frankly paranoid about their medication, which may cause decreased compliance after a medication switch. Seventy-three percent of 106 patients on atypical antipsychotics questioned in an hypothetical pharmacy setting stated they would likely not take their medication if it had been substituted for a generic by their pharmacist [94]. However, in a French study [95], 14 outpatients on Clozaril were asked by a pharmacist about switching to generic clozapine; nine patients accepted without reserve, whereas the five others required at least 15 min of explanation.

Conclusion

With 139 drug submissions to Health Canada involving generics in 2005 alone [96], the business of generic medications is expanding at a fast pace. It is imperative to question the true equivalence of generic and original medications. Generic substitution of several psychotropics has resulted in adverse consequences. Increased frequency of seizures and toxicity has been reported following generic substitution of carbamazepine, lamotrigine, and gabapentin. Different preparations of valproic acid and its derivatives may have different effectiveness and generic valproic acid may be associated with increased gastrointestinal side effects. Entry of generic formulations of newer anticonvulsants, such as lamotrigine and topiramate, has been associated with increases in dosages and/or increases in prescriptions of anticonvulsants and other medications as well as higher medical costs. Substitution of lithium preparations may lead to subtherapeutic levels. Cases of increased depressive symptomatology and/or intoxication have been reported with substitution of tricyclic antidepressants. Generic switch of fluoxetine, paroxetine, citalopram, sertraline, mirtazapine, and bupropion has been associated with increased psychopathology and/or decreased tolerability. Pharmacokinetic studies comparing generic and original venlafaxine showed significant differences in C_{max}. Among antipsychotics, concerns have centered on clozapine, with several case reports and studies reporting relapses or exacerbations of psychotic disorder following generic substitution. A study demonstrated different pharmacokinetics between a generic liquid formulation of risperidone and original tablets. Case reports have suggested clinical nonequivalence between generic and original formulations of clonazepam and alprazolam.

Our review was limited by publication bias and the heterogeneity of the studies. We chose to focus on antiepileptics commonly used in psychiatry, namely carbamazepine, valproate, lamotrigine, gabapentin, and topiramate. It is thus difficult to estimate the true

burden of consequences engendered by generic switching. Further prospective studies on the efficacy and effectiveness of generics compared to original medications are warranted. Studies for approval of generic compounds should ideally be performed not only in healthy volunteers but also in subjects representative of the clinical population and should involve therapeutic doses administered over a given time period as opposed to single dose administration. Generic pharmaceutical companies ought to continue to perform postmarketing surveillance studies to determine the true rates of adverse events with their generics. Standardization of these studies and amalgamation by national medication regulatory boards may allow for easier comparison of different formulations of a given compound.

Generic substitution may give rise to compliance issues and may not be as economically profitable as once hoped. Switching between formulations should be done on a case-by-case basis, in collaboration with the patient and with close monitoring. Physicians underestimate the frequency of generic substitution [97]. They should, along with pharmacists and patients, be sensitized to issues linked to generic substitution, especially in an era where health economics supports widespread generic use. In Quebec, pharmacists are allowed to substitute generic to original medications with the patient's consent but unbeknownst to the treating physician. Physicians can prevent generic switching by writing "do not substitute" on their prescriptions. This practice should be encouraged by the different medical associations. Alternatively, policy makers may want to review the current legislation and allow pharmacists to provide generics only when they are prescribed by the physician. Medication regulatory boards should consider adding a warning label on generic medications in order to sensitize patients to the risk of decreased tolerability and/or loss of efficacy and encourage them to report potential consequences of switching to their physician.

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Julie Eve Desmarais: Literature search, drafting article, approval of article.
Linda Beauclair: Drafting article, critical revision and approval of article.
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Conflicts of Interest

The authors declare no conflict of interests.

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